Molecular Diagnosis of thyroid cancer: What pathologists need to know

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Disclosure of Relevant Financial Relationships

Nothing to declare

Overview

1. Introduction
2. Molecular landscape of thyroid carcinoma (focus on follicular origin)
    - adult population
    - paediatric population
3. Prognosis and when should molecular testing be performed
4. Recent and new target therapies

1. Introduction

International Thyroid Cancer Incidence in 2020 GLOBOCAN Database

Incidence increasing, mortality stable (185 countries)

Global incidence

- 10.1 per 100,000 women
- 3.1 per 100,000 men

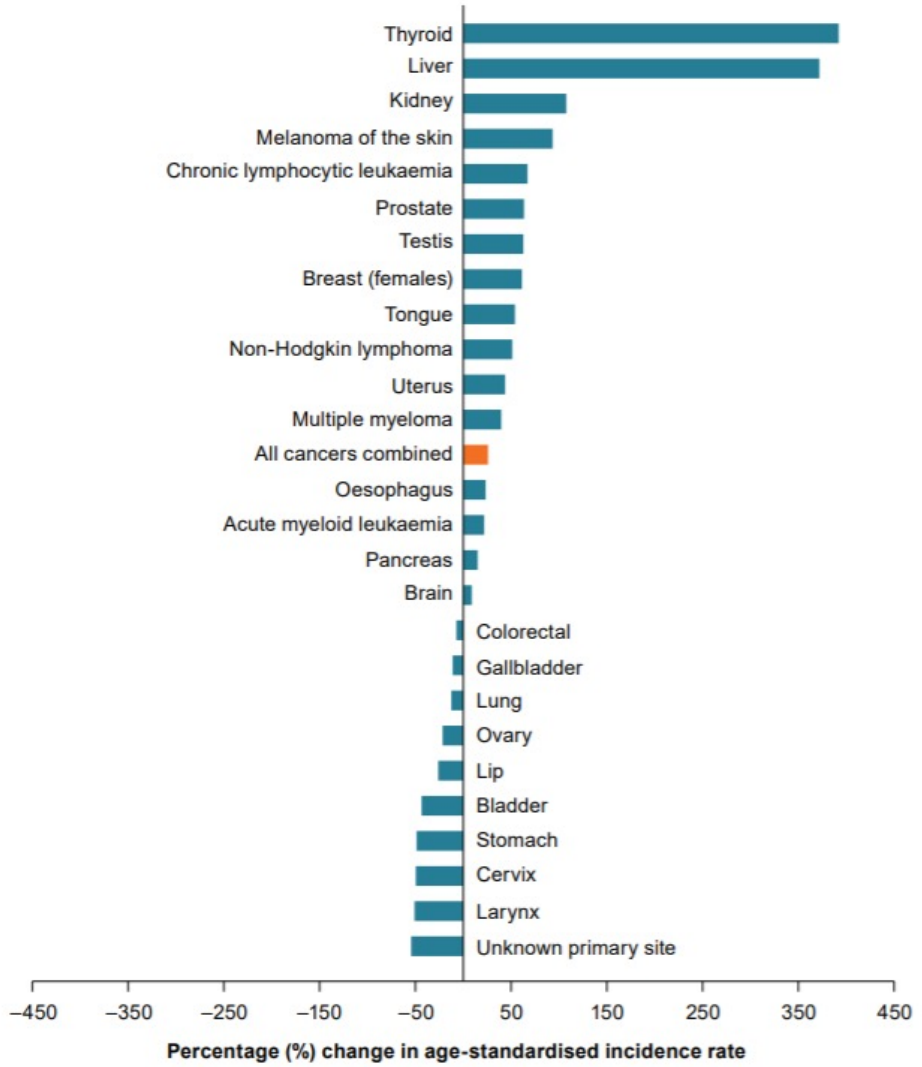
Mortality

- 0.5 per 100,000 women
- 0.3 per 100,000 men

Pizzato et al. Lancet Diabetes Endocrinology March 2022

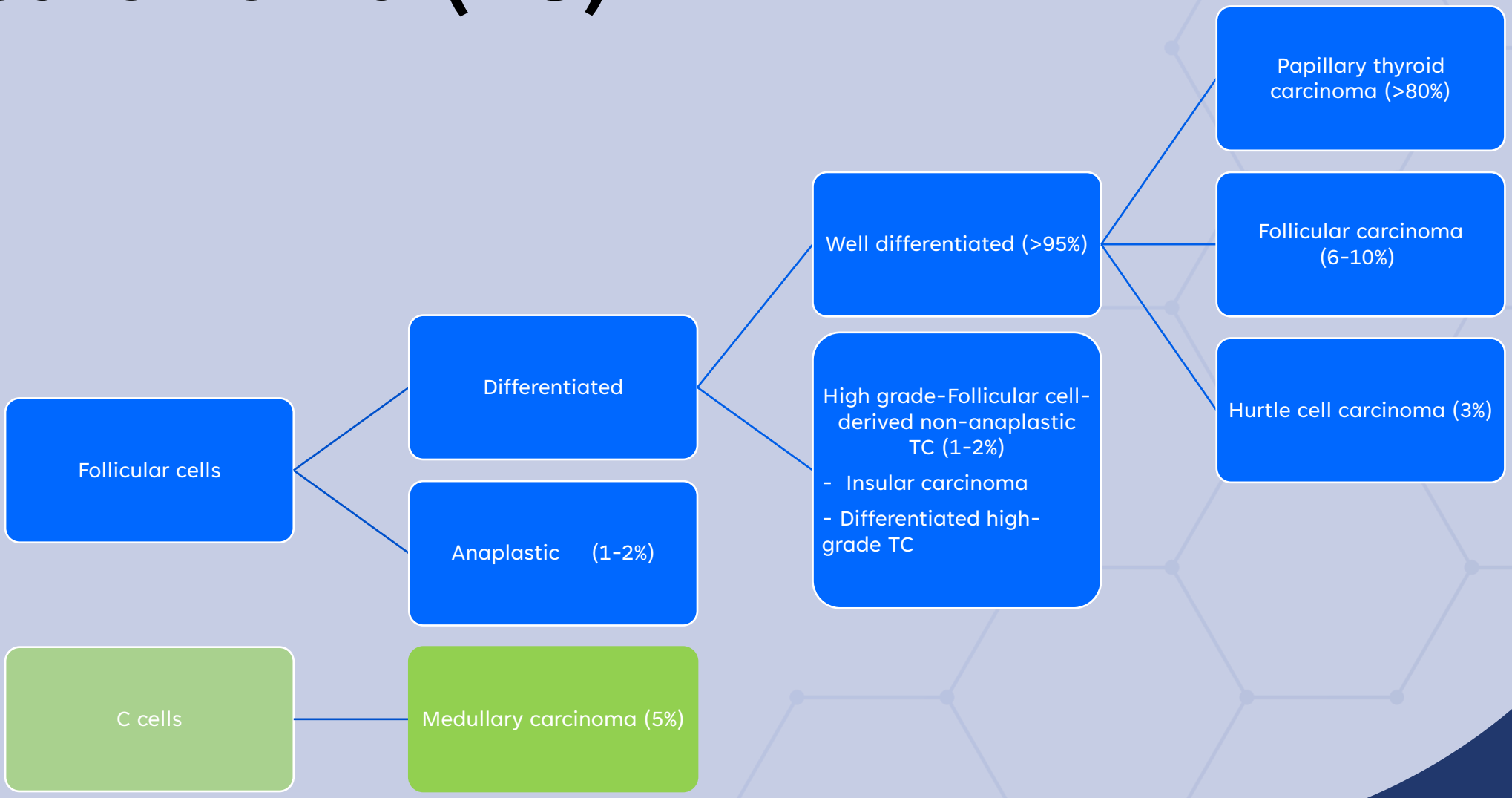
Change in incidence highest in all types of cancers in Australia

Figure 5.7: Estimated percentage change in age-standardised incidence rates for selected cancers between 1982 and 2019



AIHW (2019). *Cancer in Australia 2019*. Canberra: AIHW

Histological types of Thyroid carcinoma (TC)



2. Molecular landscape of thyroid cancer

Genetic landscape of PTC (TCGA)

- 70% classical
- 21% FV
- 7% tall cell
- 2% other

496 PTCs analyzed

Oncogenic drivers identified in **96.5%** of tumors

Mutations:

BRAF (60%) - C, tall
N/H/K RAS (12%) - FV
TERT (9%)

Fusions:

RET (6.3%)
BRAF (2.3%)
NTRK 1 (1%)
NTRK 3 (1.3%)
PPARG (1%)
ALK (0.8%)
LTK (0.3%
MET (0.3%)
FGFR2 (0.5%)
THADA (1.5%)

Low mutation burden

The Cancer Genome Atlas Research Network. *Cell*, 2014

Fusions in PTC

Across solid tumors studied in TCGA, **PTC has *the highest rate* (12%)** of recurrent oncogenic kinase fusions

Stransky, et al. *Nature Comm*, 2014

Molecular subtypes - PTC

1. BRAF-like (*BRAF*^{V600E})

2. RAS-like

The Cancer Genome Atlas Research Network. *Cell*, 2014

Signaling pathways

BRAF-like:

Activation of MAPK signaling

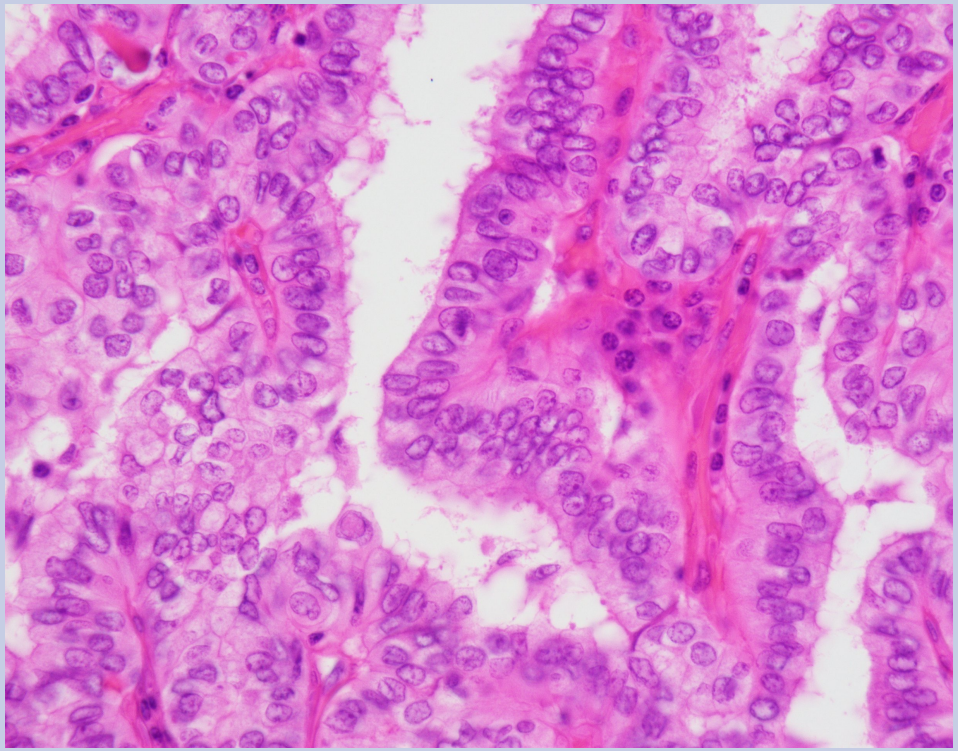
RAS-like:

Activation of both MAPK and PI3K/AKT signaling

The Cancer Genome Atlas Research Network. *Cell*, 2014

Histology

BRAF-Like



C PTC, TC PTC

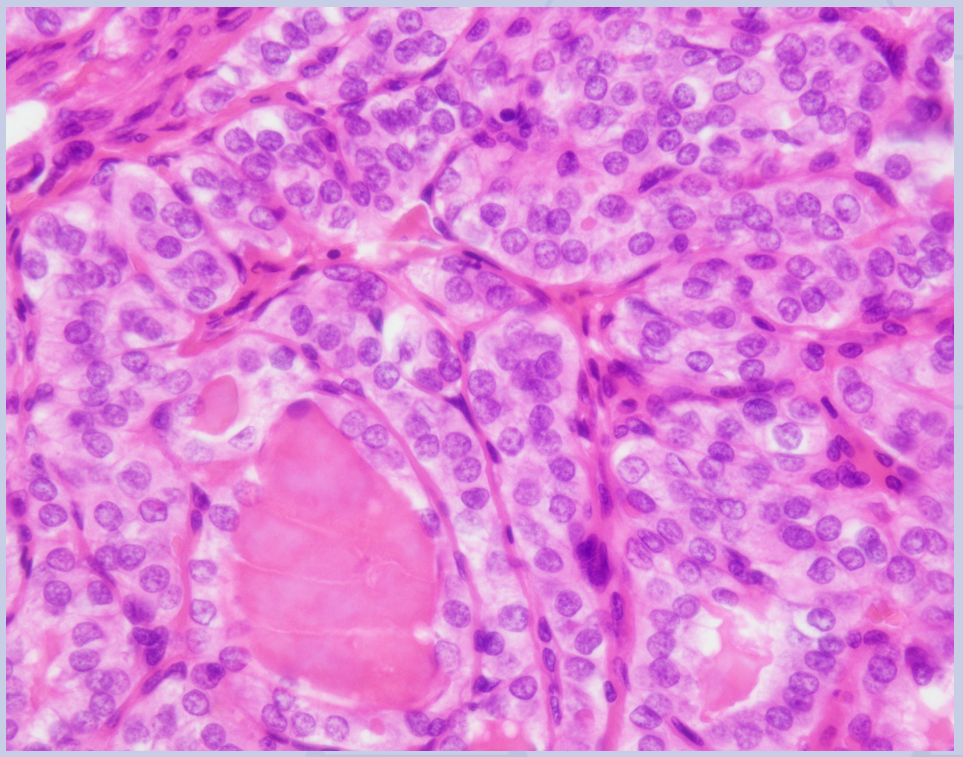
LN mets

Often ETE

Frequent tumour recurrence

More RAI refractory

RAS-Like



Less

Less LN mets

More distant metastases

More RAI responsive

Poorly differentiated and ATC

- 117 patients
- Target exome sequenceing (341 genes)
- Transcriptome (37 samples)

Landa et al. J Clin Invest. 2016; 126(3): 1052-1066

Poorly differentiated TC and ATC

- ATC higher number of mutations
- BRAF (33% vs 45%) and RAS (21% vs 18%) mutually exclusive (tumorigeneses)
- *BRAF/RAS* WT ATC: 3/10 NF1 mutation
- Gene rearrangement: 14% in PDTC, absent in ATC

  RET, PPARG, ALK

Landa et al. J Clin Invest. 2016; 126(3): 1052-1066

Poorly differentiated TC and ATC

Genes in advanced/aggressive tumours

- *EIF1AX* associated with RAS mutation. PDTC: poor survival.
- *TERT* promoter mutation in advanced tumours (40% vs 73%) – 9% in PTC
- *TP53* mutation more common in ATC (8% vs 73%)

Landa et al. J Clin Invest. 2016; 126(3): 1052-1066

Poorly differentiated and ATC

- Novel genes in cancer pathways

PI3K/ATK

SWI/SNF Switch/Sucrose Non-Fermentable nucleosome remodeling complex

HMT: histone methyltransferases

MMR: mismatch repair

Landa et al. J Clin Invest. 2016; 126(3): 1052-1066

Poorly differentiated and ATC

- BRAF-RAS score (molecular subtyping)
- All *BRAF*^{V600E} mutated PDTC and ATC were ‘BRAF-like’.
- *RAS*-mutant PDTC were ‘RAS-like’, but *RAS*-mutant ATC were ‘BRAF-like’

= ATC have high MAPK pathway activation irrespective of driver

Landa et al. J Clin Invest. 2016; 126(3): 1052-1066

3. Prognosis and when should molecular testing be done

Survival – Differentiated PTC

- Most are curable (differentiated TC) with 5 year of survival 95%

- 2% present with M1 disease with lower OS
  - OS: 40.7% vs 90.7% (P<0.001)

- Outcome of RAI response in M1 patient
  - I^{-131} responsive 72%
  - I^{-131} refractory 28%
  - OS: 92% vs 29% vs 10%

Goffredo P, et al. *World J Surg*. 2013;37:1599–1605
Durante et al. Journal of Clinical Endocrinology and Metabolism 2006.

Survival – Anaplastic carcinoma

Anaplastic thyroid carcinoma (ATC)

- Poor survival and prognosis
- Metastatic at onset >50%
- Overall survival 3-9 months depending on stage
- 1 year survival <20%

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Treatment

Most cases

1. Surgery
2. Radioactive iodine (RAI)
3. TSH suppression

RAI resistance/High grade TC/ATC

1. Focal approach: External beam radiation, RFA, cryoablation, surgery
2. Molecular therapy (MKIs, TKIs)

Molecular testing should be performed:

Molecular driver and pathology inform treatment options

4. Recent and new targeted therapy

MKI/TKI and targets

Gild M, Tsang V, Clifton-Bligh R, Robinson B. Multikinase inhibitors in thyroid cancer; Timing of targeted therapy. Nature Reviews Endocrinology 2021.

MKI – RAIR DTC

- MKI is standard of care for RAIR DTC
- low selectivity and inhibit angiogenesis by targeting VEGF receptor
- Prolong PFS
- Disease progression still occur

Molecular predictor for ($BRAF^{V600E}$, NRAS, RET)

2nd line RAIRD DTC

Redifferentiation Strategy

RAI-R DTC

- Sodium-iodide symporter (NIS) is reduced or not correctly targeted to membrane → no RAI uptake.

Redifferentiation

- Reinstitute NIS to plasma membrane
- Inhibition of the MAPK pathway through BRAF/MEK inhibitors (dabrafenib + trametinib) - short course

Clinical trials have shown success in re-differentiation in *BRAFV600E* mutants and some NRAS mutants

Fewer toxicities due to shorter term treatment

FDA approval for *BRAFV600E* solid tumours (2022)

Buffet, C et al “Redifferentiation of radioiodine-refractory thyroid cancers” *Endocrine Related Cancers*, 2020

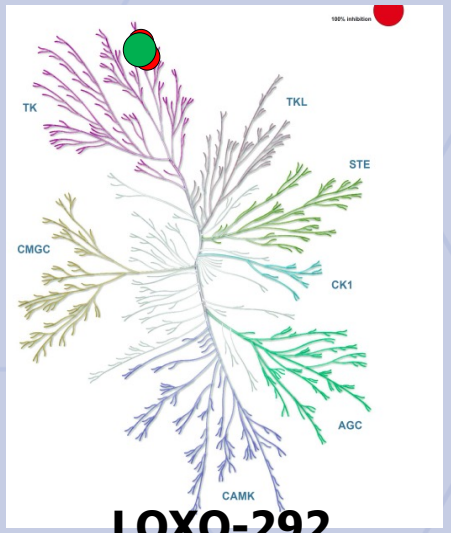
ATC BRAF V600E mutant treated with BRAF/MEK inhibitor

- Phase II trial
- 16 patients
- ORR of 69%
- 80% OS at 12 months
- FDA approved for advanced/metastatic ATC (2018)

Subbiah V et al. J Clin Oncol. 2018 Jan 1;36(1):7-13

Targeting RET

- 2 new highly potent and specific RET inhibitors
  - BLU-667
  - LOXO-292
- Both designed to potently inhibit
  - RET fusions (RAIR DTC)
  - Oncogenic RET mutations (in MTC)
- *RET* fusion mutations up to 10% of all DTC
  - More in younger patients



LOXO-292

Wirth LJ et al. 2020 Efficacy of Selpercatinib in RET-Altered Thyroid Cancers. N Engl J Med **383**:825-835

Subbiah V, et al. 2021 Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study. The lancet Diabetes & endocrinology **9**:491-501

LOXO-292 Selpercaptinib: LIBRETTO

papillary (in 13 patients [68%]), poorly differentiated (in 3 [16%]), anaplastic (in 2 [11%]), and Hurthle cell (in 1 [5%])

NTRK rearranged PTCs respond to TRK inhibitor Larotrectinib

Phase 2 trial

5 *NTRK* fusion positive PTC

100% response

Clinical Case Reports

Open Access

CASE REPORT | Open Access

Complete response to larotrectinib treatment in a patient with papillary thyroid cancer harboring an *ETV6-NTRK3* gene fusion

Fabián Pitoia

First published: 20 February 2021 | https://doi.org/10.1002/ccr3.3900

JCO Precision Oncology > List of Issues > Volume 6 >

CASE REPORTS

Real-World Experience of *NTRK* Fusion–Positive Thyroid Cancer

An impressive response with larotrectinib in a patient with a papillary thyroid carcinoma harboring an *SQSTM1–NTRK1* fusion Get access >

Sophie Bargas, Anne Mc Leer, Julie Mondet, Olivier Chabre, Mathieu Laramas

European Journal of Endocrinology, Volume 186, Issue 4, Apr 2022, Pages K5–K8,

Drilon A et al. N EnglJ Med. 2018 Feb 22;378(8):731-739

SUMMARY

- Incidence of PTC is rising with stable mortality but metastatic, RAI-R disease do worse
- Molecular testing requested on all RAI-R TC, HGTC, MTC
- RNSH experience
    - 87% had actionable alteration
    - 57% FDA approved drug
- Clinical trial where molecular targets are available

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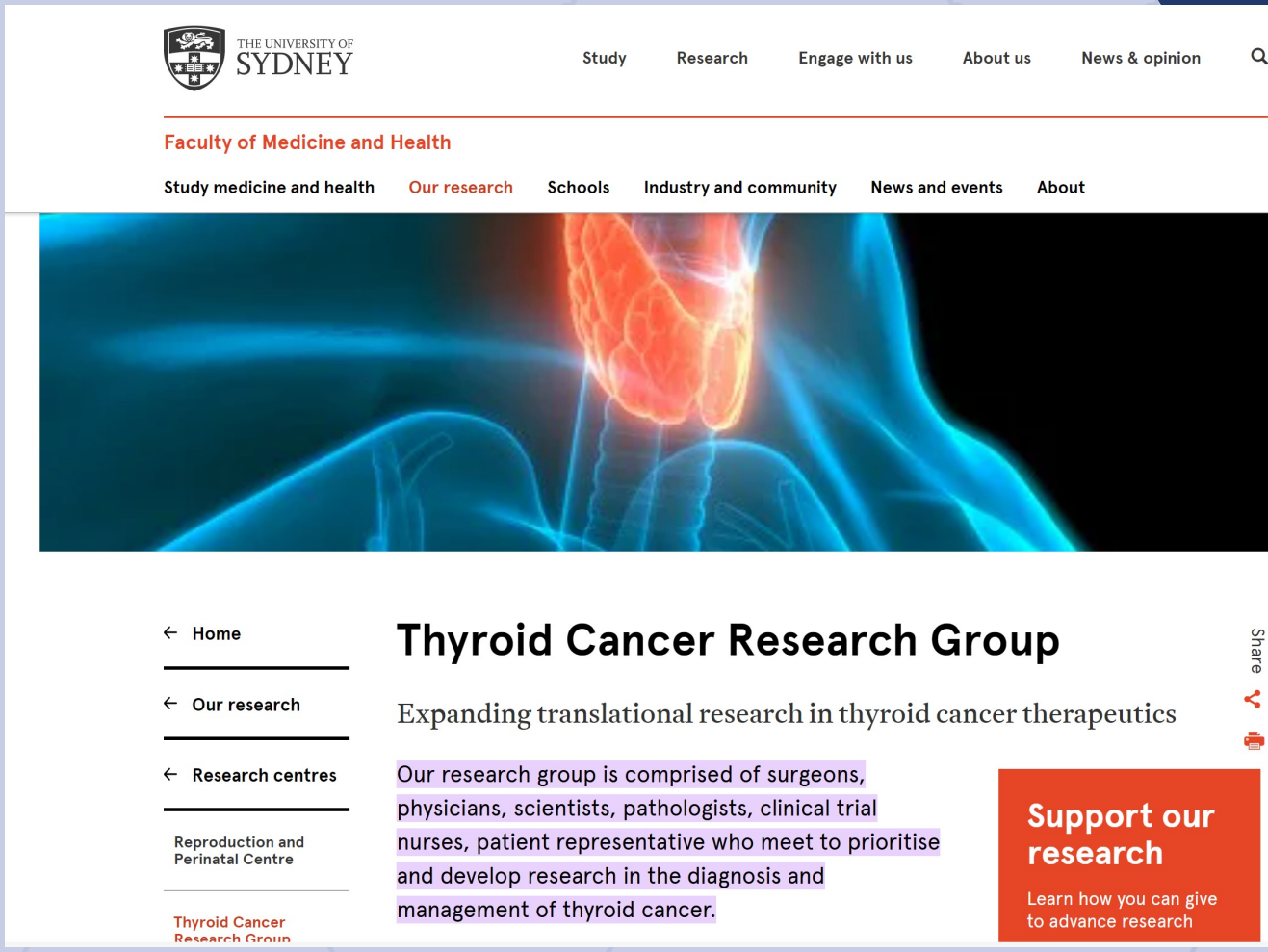

Thank you